BOARD OF PATENT APPEALS AND INTERFERENCES
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In re patent application of:	)	Before the Examiner
Stefano Carlino	)	Elli Peselev
	)	
Serial No. 10/523,657	)	Group Art Unit: 1623
	)	
Filing Date: February 4, 2005	)	Attorney Docket: LABM-10
	)	
PROCESS FOR PREPARING A STERILE HIGH MOLECULAR WEIGHT HYALURONIC ACID FORMULATION	)	May 14, 2010

REPLY BRIEF (37 C.F.R. §41.37)

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P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is in reply to the Examiner's Answer filed in this case on February 17, 2010. The time to file this Reply Brief has been extended to July 17, 2010, by Applicant's Petition under 37 CFR §41.41(c).

I hereby certify that, on the date shown below, this correspondence is being deposited with the United States Postal Service in an envelope addressed to Board of Patent Appeals and Interferences, P.O. Box 1450, Alexandria, VA 22313-1450 as "Express Mail Post Office to Addressee."

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May 14, 2010
Date

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II. TABLE OF AUTHORITIES
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None.

III. STATEMENT OF ADDITIONAL FACTS
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None.

IV. ARGUMENT
(37 C.F.R. §41.41(5))

The arguments put forward by the Applicant in the Appeal Brief are maintained. Further, in response to the specific arguments made by the Examiner in his "Response to Argument" in the Examiner's Answer, the following is additionally submitted.

(1) In the Examiner's "Response to Argument" in respect of the Examiner's rejection of claims 1 and 4-9 on grounds of non-statutory obviousness-type double patenting over the claims 1-23 of US 6,489,467 (Carlino et al.) in view of US 5,503,848 (Perbellini et al.) the Examiner asserts that *"it is the Examiner's position that the disclosure by Perbellini et al. of dissolving hyaluronic acid in water in a suitable apparatus, equipped with a heating system and vacuum so as to achieve a concentration ranging between and 1 mg/ml and 40 mg/ml reads on the claimed step of concentrating an aqueous formulation by applying a vacuum until a desired concentration is achieved"*. This objection is respectfully traversed.

Perbellini et al. recites that "high hyaluronic acid...is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" in an apparatus equipped with a "vacuum/nitrogen pressure/sterile filtrate system". It is a mere assertion by the Examiner that this apparatus of Perbellini et al. *"reads onto the claimed step of concentrating an aqueous formulation by applying a vacuum until a desired concentration is achieved."* The Examiner has not even

established that the vacuum/nitrogen pressure/sterile filtrate system of Perbellini et al. functions as a vacuum concentration system.

In chemical processes, vacuums are used for a number of different purposes, for instance (i) for providing a reduced pressure on one side of a filter in order to pull filtrate through the filter in filtration processes; (ii) for creating reduced air pressure atmosphere in the drying or storage of air/oxygen sensitive chemical products; (iii) for providing reduced pressure in a reaction chamber in order to reduce boiling temperature of a liquid, in vacuum concentration processes. It is clear that the fact an apparatus includes a system which can provide a vacuum does not mean that the apparatus is intended for, or even suitable for, carrying out a vacuum concentration process.

In the present case, the apparatus described in Perbellini et al. with a "vacuum/nitrogen pressure/sterile filtrate system" has both nitrogen pressure and vacuum, and is by definition a flow-through system (whereby nitrogen pressure applied on one side of a filter, is used to push solution through the filter and a vacuum, applied on the opposite side of the filter, is used to pull filtrate through the filter), as used in conventional filtration processes with filters having small pore size and/or for filtration of viscous solutions, and is not a vacuum concentrating system.

The nitrogen pressure/vacuum/sterile filtration system cannot be a vacuum concentrating apparatus, since the apparatus provides for both nitrogen pressure and

vacuum. In a vacuum concentration apparatus it is necessary to create a reduced pressure atmosphere in the reaction chamber in order to lower the boiling temperature of a liquid to be concentrated, contained in the reaction chamber. It would be complete nonsense to introduce a gas under pressure, i.e. nitrogen pressure, to a reaction chamber in which it is desired to establish a low pressure, as required for vacuum concentration processes.

It is clear that the apparatus described in Perbellini et al. is a filtration apparatus, and cannot function as a vacuum concentration system.

In the process of Perbellini et al., the vacuum/nitrogen pressure/sterile filtrate system serves only to effect the filtration of the high hyaluronic acid solution through a sterilizing membrane, having a porosity of 0.2 μm (US 5,503,848, col. 10 lines 28-32). It is to be remembered that in order to achieve filtration of aqueous solutions of hyaluronic acid through such microporous sterilizing membranes (e.g. porosity 0.2 μm), it is necessary to carry out the filtration using nitrogen pressure and/or vacuum conditions, otherwise the aqueous hyaluronic acid solution will not pass through the micorporous membrane.

Moreover, it is noted that even the name of the system recited in Perbellini et al., "vacuum/nitrogen pressure/sterile filtrate system" implies that the system is a filtration system (i.e. a flow-through system) and not a vacuum concentration apparatus.

With respect to the presence of a heating system in the apparatus of Perbellini et al., it is noted that it is conventional practise in dissolution processes to heat the solution in order to increase solubility of solutes in solution. Accordingly, it is respectfully submitted that the heating system re-cited in Perbellini et al. at column 10, line 22, serves the purpose of permitting heating in order to increase solubility of the hyaluronic acid, or the estereal derivative of hyaluronic acid, if necessary in order to dissolve the hyaluronic acid, or its estereal derivative, to a concentration in the range of 1 mg/ml to 40 mg/ml. The presence of a heating system does not imply in any way a vacuum concentration step.

Furthermore, it is again highlighted that Perbellini et al. merely teaches that "hyaluronic acid... is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" in the apparatus. The process taught by Perbellini et al. merely involves dissolving hyaluronic acid in water up to a concentration in the range of 1 mg/ml to 40 mg/ml. There is no disclosure whatsoever of any step of concentrating a hyaluronic acid solution to a specified accurate concentration by a vacuum concentration method.

Accordingly, it is clear that Perbellini et al. does not describe any step of concentrating an aqueous formulation of hyaluronic acid under vacuum. Nor does Perbellini et al. disclose, or suggest in any way, a step of concentrating an aqueous formulation of high molecular weight hyaluronic acid by applying a vacuum and

boiling off water until the specified pharmaceutical concentration is reached, as required by the pending claims.

Finally, it is highlighted that Perbellini et al. teaches that hyaluronic acid is dissolved in water, to a concentration ranging between 1 mg/ml and 40 mg/ml, in a first step, followed by filtration of the hyaluronic acid solution through a sterilizing membrane with porosity 0.2 μm in a subsequent step. There is clearly no disclosure whatsoever in Perbellini et al. of any step of concentration of a filter-sterilized solution of HA, by applying a vacuum and boiling off water until a specified concentration is reached, as required by the pending claims.

(2) In the Examiner's "Response to Argument" with respect to his rejection of claims 1 and 4-9 on grounds of obviousness under 35 U.S.C. 103(a) over Carlino et al. (WO 00/44925 or US 6,489,467) in view of Perbellini et al. (US 5,503,848), the Examiner states *"it is the Examiner's position that the teaching by Perbellini et al. in column 10 of dissolving hyaluronic acid in an apparatus equipped with a heating system and a vacuum reads on the claimed step of concentrating aqueous formulation of hyaluronic acid under vacuum."* This objection is respectfully traversed.

First, it is highlighted that Perbellini et al. recites that "hyaluronic acid...is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" in an apparatus equipped with a "vacuum/nitrogen

pressure/sterile filtrate system." It is a mere assertion by the Examiner that this apparatus of Perbellini et al. *"reads onto the claimed step of concentrating an aqueous formulation of hyaluronic acid under vacuum."* The Examiner has not even established that the vacuum/nitrogen pressure/sterile filtrate system of Perbellini et al. functions as a vacuum concentration system.

In chemical processes, vacuums are used for a number of different purposes, for instance (i) for providing a reduced pressure on one side of a filter in order to pull filtrate through the filter in filtration processes; (ii) for creating reduced air pressure atmosphere in the drying or storage of air/oxygen sensitive chemical products; (iii) for providing reduced pressure in a reaction chamber in order to reduce boiling temperature of a liquid, in vacuum concentration processes. It is clear that the fact an apparatus includes a system which can provide a vacuum does not mean that the apparatus is intended for, or even suitable for, carrying out a vacuum concentration process.

In the present case, the apparatus described in Perbellini et al. with a "vacuum/nitrogen pressure/sterile filtrate system" has both nitrogen pressure and vacuum, and is by definition a flow-through system (whereby nitrogen pressure applied on one side of a filter, is used to push solution through the filter and a vacuum, applied on the opposite side of the filter, is used to pull filtrate through the

filter), as used in conventional filtration processes with filters having small pore size and/or for filtration of viscous solutions, and is not a vacuum concentrating system.

The nitrogen pressure/vacuum/sterile filtration system cannot be a vacuum concentrating apparatus, since the apparatus provides for both nitrogen pressure and vacuum. In a vacuum concentration apparatus it is necessary to create a reduced pressure atmosphere in the reaction chamber in order to lower the boiling temperature of a liquid to be concentrated, contained in the reaction chamber. It would be complete nonsense to introduce a gas under pressure, i.e. nitrogen pressure, to a reaction chamber in which it is desired to establish a low pressure, as required for vacuum concentration processes.

It is clear that the apparatus described in Perbellini et al. is a filtration apparatus, and cannot function as a vacuum concentration system.

In the process of Perbellini et al., the vacuum/nitrogen pressure/sterile filtrate system serves only to effect the filtration of the high hyaluronic acid solution through a sterilizing membrane, having a porosity of 0.2 μm (US 5,503,848, col. 10 lines 28-32). It is to be remembered that in order to achieve filtration of aqueous solutions of hyaluronic acid through such microporous sterilizing membranes (e.g., porosity 0.2 μm), it is necessary to carry out the filtration using nitrogen pressure and/or vacuum conditions, otherwise the aqueous hyaluronic acid solution will not pass through the micorporous membrane.

Moreover, it is noted that even the name of the system recited in Perbellini et al., "vacuum/nitrogen pressure/sterile filtrate system" implies that the system is a filtration system (i.e. a flow-through system) and not a vacuum concentration apparatus.

With respect to the presence of a heating system in the apparatus of Perbellini et al. it is noted that it is conventional practice in dissolution processes to heat the solution in order to increase solubility of solutes in solution. Accordingly, it is respectfully submitted that the heating system re-cited in Perbellini et al. at column 10, line 22, serves the purpose of permitting heating in order to increase solubility of the hyaluronic acid, or the estereal derivative of hyaluronic acid, if necessary in order to dissolve the hyaluronic acid, or its estereal derivative, to a concentration in the range of 1 mg/ml to 40 mg/ml. The presence of a heating system does not imply in any way a vacuum concentration step.

Furthermore, it is again highlighted that Perbellini et al. merely teaches that "hyaluronic acid... is dissolved in water for injectable preparations, so as to reach a concentration ranging between 1 mg/ml and 40 mg/ml" in the apparatus. The process taught by Perbellini et al. merely involves dissolving hyaluronic acid in water up to a concentration in the range of 1 mg/ml to 40 mg/ml. There is no disclosure whatsoever of any step of concentrating a hyaluronic acid solution to a specified accurate concentration by a vacuum concentration method.

Accordingly, it is clear that Perbellini et al. does not describe any step of concentrating an aqueous formulation of hyaluronic acid under vacuum. Nor does Perbellini et al. disclose, or suggest in any way, a step of concentrating an aqueous formulation of high molecular weight hyaluronic acid by applying a vacuum and boiling off water until the specified pharmaceutical concentration is reached, as required by the pending claims.

Furthermore, it is highlighted that Perbellini et al. teaches that hyaluronic acid is dissolved in water to a concentration ranging between 1 mg/ml and 40 mg/ml in a first step, followed by filtration of the hyaluronic acid solution through a sterilizing membrane with porosity 0.2 μm in a subsequent step. There is clearly no disclosure whatsoever in Perbellini et al. of any step of concentration of a filter-sterilized solution of HA, by applying a vacuum and boiling off water until a specified concentration is reached, as required by the pending claims.

Second, the Examiner further objects that Perbellini et al. describes the parcelling of the filtered solution into sterile containers, and asserts that *"it would have been obvious to a person having ordinary skill in the art to immediately use the purified hyaluronic acid and only freeze-drying hyaluronic acid for long storage use."* This objection is respectfully traversed.

It is respectfully submitted that Perbellini et al. specifically teach away from the use of hyaluronic acid in solution form. Perbellini et al. is directed to the

preparation of discs of a spongy material consisting essentially of lyophilized hyaluronic acid, or its estereal derivatives, for use in microsurgical practise, particularly for use in the repair of tympanic perforations or lesions. Perbellini et al. specifically teaches that spongy disc preparations of lyophilized hyaluronic acid should be used in order to avoid problems related to the use of hyaluronic acid in solution form, such as humidification of the area to be treated therefore causing steeping; and too short stay-time of the hyaluronic acid on the lesion therefore requiring repeated administration with the associated risks of causing new traumas in the tympanic membrane on application, or that the optimum application conditions in asepsis is not respected (see column 2, line 63, to column 3, line 11, of Perbellini et al.). Accordingly, the skilled person on reading Perbellini et al. is specifically taught away from the use of hyaluronic acid solutions, and accordingly would have no motivation to use the hyaluronic acid in the form of the filtered solution intermediate, but would use only the lyophilized spongy disc product taught by Perbellini et al.

Moreover, it is pointed out that in Perbellini et al. hyaluronic acid is dissolved in water into concentration in range 1-40 mg/ml a first step, followed by filtration of HA solution through a 0.2 μm filter in a second step, and then directly after the filtration step the filtered solution is parcelled into sterile containers in a third step for the lyophilisation process. Accordingly, Perbellini et al. does not

provide any teaching whatsoever for a step of filling a pharmaceutical formulation of HA directly after a concentration step into sterile recipients for pharmaceutical use, as required by the pending claims.

Furthermore, it is again highlighted that in the dissolution step of Perbellini et al. it is taught only that HA is dissolved in water up to a concentration in the range of 1 mg/ml to 40 mg/ml and there is no teaching whatsoever of providing a solution of a specified accurate concentration of hyaluronic acid, even in this dissolution step. Moreover, it is highlighted that the filter-sterilized solution of hyaluronic acid obtained by the solution filtration step of Perbellini et al. could not be a pharmaceutical formulation comprising an accurate specified concentration of high molecular weight hyaluronic acid salt (HA), as required by the pending claims, also since in the filtration step of Perbellini et al., if Perbellini et al. were to use high molecular weight hyaluronic acid (as required for the sterile pharmaceutical formulations of the present invention), then at the concentrations of high molecular weight HA required for providing the high viscosity aqueous HA formulations for pharmaceutical use (e.g. having 1 to 3 % wt/v HA) not all the HA would pass through the 0.2 μm pore size filter of Perbellini et al. This would result in a significant reduction of the concentration of HA. Accordingly, the resultant filtered solution would not have an accurate specified concentration, as required by the pending claims.

In view of the above, the Examiner's rejection of pending claims 1 and 4-9 on the grounds of non-statutory double patenting over Carlino et al. (US 6,489,467), or alternatively on grounds of obviousness under 35 USC 103(a) over Carlino et al. (WO 00/44925 or US 6,489,467) in view of Perbellini et al. (US 5,503,848) is respectfully traversed.

Respectfully submitted,

Date: May 14, 2010

By: _____

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